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A Role for Cellular Prion Protein in Late-Onset Alzheimer's Disease: Evidence from Preclinical Studies

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Review of Salazar et al.

Alzheimer's disease (AD), the most prevalent form of dementia, affects 1 in 9 individuals >65 years old (Alzheimer's Association, 2016). Cognitive decline is the most distinctive symptom of AD, and it strongly correlates with synapse loss (Masliah et al., 1990; Terry et al., 1991). Currently, there is no effective strategy to halt or revert AD progression in patients; this can be partially attributed to the yet incipient knowledge of pathophysiological processes underlying disease progression.

The two major histopathological markers of AD are intracellular neurofibrillary tangles, formed by tau protein in its hyperphosphorylated form and extracellular plaques, composed of amyloid-β (Aβ) peptides. Aβ peptide assembles into aggregates of various sizes, ranging from oligomers to fibrils, but soluble oligomers (AβOs) are most strongly correlated with disease severity (Bjorklund et al., 2012; Bilousova et al., 2016). In the last couple of decades, AβOs have consistently been found to be associated with synapse failure and loss, as well as with the memory decline germane to AD pathology (for review, see Ferreira et al., 2015). More recently, AβOs were shown to induce neuroinflammatory processes in AD brains, thereby influencing synaptic pruning and cognition (Hong et al., 2016; for review, see Santos and Ferreira, 2017). Importantly, pharmacological alleviation of AβO-induced inflammation is sufficient to prevent cognitive impairment in murine models of AD, indicating that inflammation is central to pathological processes (Ledo et al., 2016).

An intriguing aspect of AβOs is their capacity to bind to synaptic terminals and trigger neurotoxic signaling that leads to synaptic failure. On the quest to find potential "AβO receptors" at synapses, more than a dozen molecules have been shown to interact with AβOs (for review, see Ferreira et al., 2015). Notably, the cellular prion protein (PrP^C) has high affinity for AβOs (Laurén et al., 2009). PrP^C is a glycosylphosphatidylinositol-anchored protein localized to the plasma membrane, and it is expressed in most cell types in mammals, but particularly enriched in the nervous system (for review, see Linden et al., 2008). Although known to turn into a misfolded version that causes neurodegeneration in transmissible spongiform encephalopathies, PrP^C is thought to be involved in several normal physiological processes, such as multiprotein complex formation on the cell surface (for review, see Castle and Gill, 2017). However, the role of PrP^C in synaptic plasticity remains controversial. An early report from Collinge et al. (1994) showed that hippocampal LTP was impaired in PrP^C-null mice. Consistent with this, another report indicated that PrP^C deletion alters neuronal excitability in hippocampal CA1 (Mallucci et al., 2002). However, Lledo et al. (1996) reported that PrP^C deletion had no effects on hippocampal LTP formation.

Although AβOs may lead to memory failure through multiple mechanisms (Balducci et al., 2010), their interactions with PrP^C have been shown to mediate aberrant signaling pathways, synapse loss, and cognitive decline in AD models (for review, see Salazar and Strittmatter, 2017). Binding of AβOs to PrP^C recruits Type 5 metabotopic gluatamate receptors (mGluR5) to abnormally activate Fyn kinase and impair synapse function (Um et al., 2012; Haas and Strittmatter, 2016). These results have raised the important question of whether interfering with AβO-PrP^C interactions could mitigate AD phenotypes and rescue memory. Interestingly, endogenous or synthetic ligands of PrP^C interrupt AβO-mediated signaling and prevent neurotoxicity in neurons (Haas et al., 2014; Beraldo et al., 2016). Nonetheless, therapeutic implications and detailed mechanisms linking PrP^C to AD progression still remain to be determined.

A recent report published in *The Journal of Neuroscience* has investigated the effects of PrP^C ablation in advanced stages of AD (Salazar et al., 2017). Salazar et al. (2017) crossed mice that express AD-linked mutated genes (APP/PS1) with a strain in which *Prnp*, the gene encoding to PrP^C,

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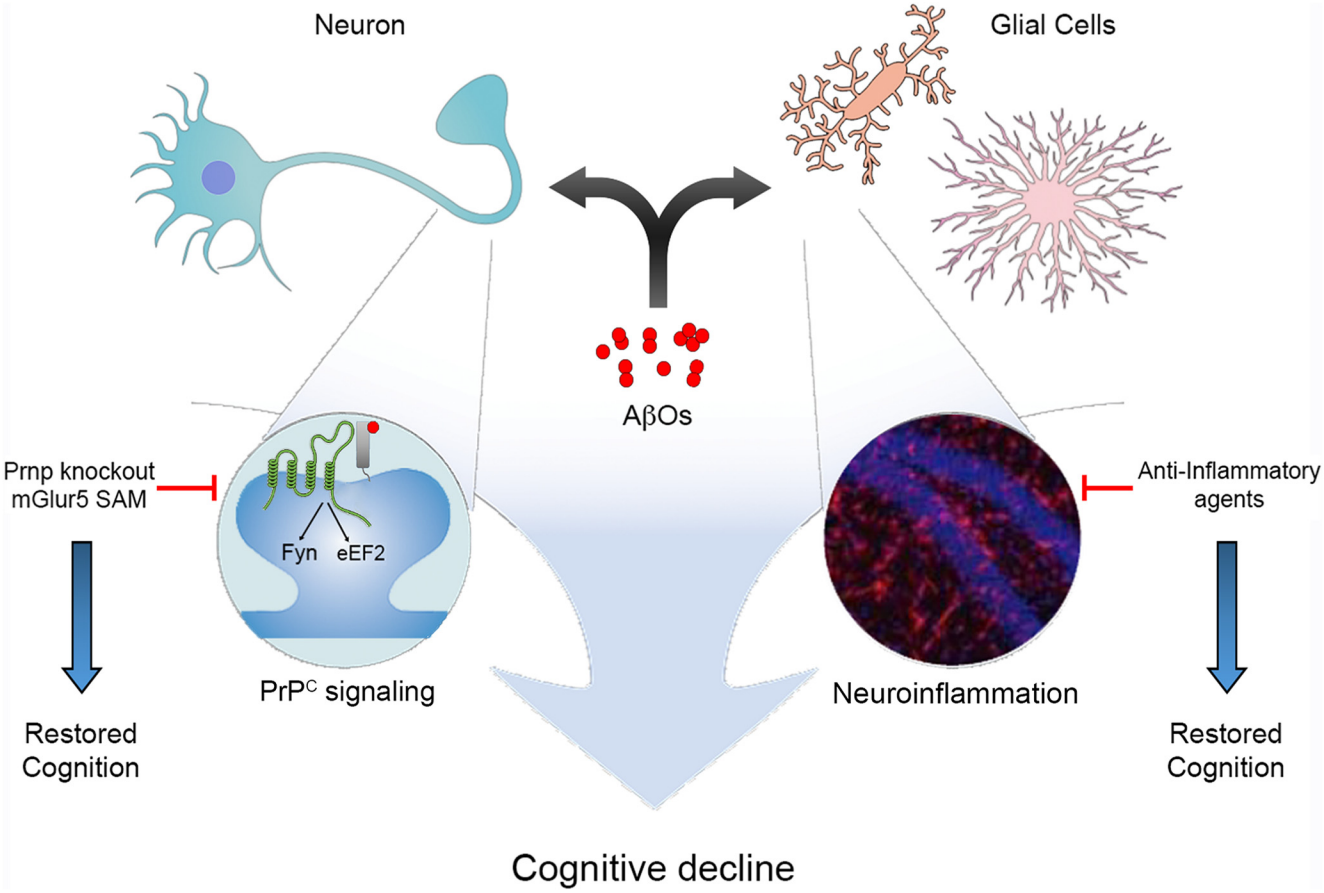

Figure 1. Aβ0-induced PrP^C signaling and neuroinflammation converge to cause cognitive decline. AβOs can bind to and trigger abnormal signaling cascade in both neurons and glial cells. At synapses, AβOs bind to PrP^C and recruit mGluR5, forming a multiprotein complex. This complex signals to increase activation of Fyn and inactivation of eEF2, resulting in reduced protein synthesis. Depletion of PrP^C, pharmacological modulation of mGluR5 by using Silent Allosteric Modulation (SAM) or inhibition of Fyn restores cognition. AβOs also induce neuroinflammation, which also leads to cognitive decline. Anti-inflammatory agents, on the other hand, can rescue cognition. Thus, neuroinflammation and PrP^C may be convergent or parallel pathways leading to cognitive decline in AD. Neurons and glial cells were adapted from the software Mind The Graph. Left Inset, Expanded view of the synapse, showing Aβ0-PrP^C-mGluR5 activity leading to Fyn activation and eEF2 inactivation. Right Inset, Reprinted with permission (Ledo et al., 2016). Hippocampal slice treated with AβOs and immunostained for Iba-1 and DAPI, showing pronounced microgliosis.

could be conditionally knocked out by administering tamoxifen. Using these mice enabled the authors to isolate the role of PrP^C in disease progression without disrupting any possible function during normal development or the onset of pathology.

Salazar et al. (2017) investigated the effects of *Prnp* deletion in mice at 12 and 16 months of age by measuring performance in a water maze test before and after treating mice with tamoxifen to delete *Prnp*. Before treatment with tamoxifen, 12-month-old APP/PS1 showed greater latency to find the hidden platform than WT mice. Remarkably, the tamoxifen administration rescued impaired memory of both 12- and 16-month-old APP/PS1 mice in cognitive tests (Salazar et al., 2017). This indicates that blocking the action of PrP^C may be a promising strategy to rescue cognition in late-onset AD. Furthermore, conditional deletion of *Prnp* rescued synapse loss in 12- and 16-month-old APP/PS1 mice, as measured by levels of the synaptic proteins PSD-95 and SV2A (Salazar et al., 2017). Therefore, the interaction between PrP^C and AβOs appears to be involved in maintaining cognitive impairment in later stages of AD, making it an attractive therapeutic target.

The interaction between PrP^C and mGluR5 has previously been shown to play a key role in the persistence of LTD in AD models (Hu et al., 2014). The PrP^C-mGluR5 complex, triggered by AβOs, promotes phosphorylation of eukaryotic elongation factor 2 (eEF2). This results in impaired protein synthesis and preferential translation of so-called "LTD proteins" that orchestrate synaptic weakening and loss (Um et al., 2013). Importantly, Salazar et al. (2017) showed that ablation of PrP^C in APP/PS1 mice blocks increased phosphorylation of eEF2, which might result in restoration of protein synthesis, thereby restoring neuronal activity to a basal state. Preclinical evidence indicates positive effects of modulating mGluR5-Fyn-eEF2 signaling pathways in AD models (Kaufman et al., 2015; Haas et al., 2017); thus, the development of pharmacological modulators is expected to test the clinical relevance of these findings.

Notably, the late removal of *Prnp* gene at 12 months altered neither soluble nor insoluble Aβ species in APP/PS1 mouse brains (Salazar et al., 2017). This corroborates previous findings from the same group showing that *Prnp* knock-out did not affect Aβ levels (Gimbel et al., 2010) and suggests that PrP^C does not contribute to AD pathology by altering amyloid burden. Nevertheless, it is possible that PrP^C deletion influences tau hyperphosphorylation because Fyn has been linked to somatodendritic accumulation of Tau (Li and Götz, 2017). Data showing a positive effect of PrP^C deletion on tau hyperphosphorylation may reinforce the potential of a therapeutic strategy that targets AβO-PrP^C-mGlur5 interaction.

In line with previous findings (Gimbel et al., 2010), Salazar et al. (2017) observed no changes in either astrogliosis or microgliosis after PrP^C deletion in aged APP/PS1 mice. Therefore, PrP^C appears not to

be involved in the neuroinflammatory process in AD brains. Notably, Haas et al. (2017) reported that pharmacological modulation of the interaction between mGluR5 and PrP^C did not alleviate astrocytosis and microgliosis of APP/PS1 mice, although it rescued cognitive impairment in these mice. These data point toward the possibility that neuroinflammation and PrP^C-mGluR5 comprise parallel pathways downstream of Aβ accumulation converging on synapse failure and cognitive decline (Fig. 1). Importantly, it was recently observed that treatment with ibuprofen, a nonsteroidal anti-inflammatory drug, prevents cognitive decline in APP/PS1 mice independently of reduction of inflammatory markers: instead, it changed the expression of synaptic plasticity-related genes (Woodling et al., 2016). The possibility that inflammatory and mGluR5-PrP^C processes act in synergy suggests that simultaneously targeting these processes would be beneficial, opening a novel approach to halt AD progression.

In conclusion, evidence provided by Salazar et al. (2017) indicates that late depletion of PrP^C rescues cognition in APP/PS1 mice. Importantly, the results show that ablation of PrP^C after disease onset has this beneficial effect on cognition, without changing major disease hallmarks. The collection of preclinical findings regarding the importance of the PrP^C-mGluR5 pathway in AD positions PrP^C as an attractive therapeutic target and should encourage further steps toward clinical trials.

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